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**METHODS AND APPARATUS FOR ENHANCED AND CONTROLLED
DELIVERY OF A BIOLOGICALLY ACTIVE AGENT INTO THE
CENTRAL NERVOUS SYSTEM OF A MAMMAL**

CROSS REFERENCE TO RELATED APPLICATIONS:

1-18-05
This application is a continuation-in-part (CIP) of U.S. Ser. No. 09/197,133 filed November 20, 1998 ^{which is a con.} ~~as a U.S. national phase entry~~ of PCT/EP96/05086 of November 19, 1995. This is one of two simultaneously filed CIPs of the '133 application.

FIELD OF THE INVENTION

The present invention relates to delivery methods and devices for effectively introducing a biologically active agent into deeper layers of the mammalian central nervous system (CNS). More specifically the invention relates to both invasive and non-invasive methods and devices for enhanced and controlled delivery of said agents into the mammalian CNS while circumventing the blood-brain barrier (BBB).

BACKGROUND OF THE INVENTION

A variety of approaches currently exist for delivering biologically active agents to the CNS. These include, among possible others, oral administration, intravenous -, intramuscular - and transcutaneous administration. All of the above drug delivery approaches tend to be systemic. Meaning that the drug is delivered into the systemic circulation, being carried to all internal organs and tissues and it has to pass through the blood-brain barrier (BBB) in order to access the CNS. Obviously, all other organs are being exposed to the drug, which may lead to a high incidence of side effects, particularly with those medications toxic to certain organs (e.g. nephrotoxic, hepatotoxic etc.). Most importantly, the therapeutic efficacy of numerous highly effective biologically active agents (e.g. large compounds, hydrophilic and charged substances such as peptides) is restricted, because they cannot or poorly penetrate the BBB, resulting in sub-therapeutic brain levels of these substances. High systemic levels have to be